

What is claimed is

1. A transgenic mouse comprising as a translocus a YAC of about 410 Kb, wherein the YAC contains most of the human V $\lambda$  genes of cluster A and all the human J $\lambda$ - C $\lambda$  segments in germline configuration, wherein the translocus shows high expression, and is able to compete equally with the endogenous mouse  $\kappa$  locus.
2. A transgenic mouse comprising as a translocus a YAC of about 410 Kb, wherein the YAC contains most of the human V $\lambda$  genes of cluster A and all the human J $\lambda$ - C $\lambda$  segments in germline configuration, wherein the mouse has one or both endogenous Ig $\kappa$  alleles disrupted, and wherein the translocus shows high expression.
3. A transgenic mouse carrying a 380 Kb region of the human immunoglobulin (Ig)  $\lambda$  light (L) chain locus in germline configuration, wherein the introduced translocus resides on a yeast artificial chromosome (YAC) that accommodates the most proximal V (variable gene)  $\lambda$  cluster - with 15 V  $\lambda$  genes that contribute to over 60% of  $\lambda$  light chains in man - and all J  $\lambda$ - C  $\lambda$  segments with the 3' region including the downstream enhancer.
4. A transgenic mouse comprising human Ig lambda genes in which the proportion of the  $\kappa$  and  $\lambda$  light chains expressed by said human lambda genes

resembles that found in humans, and exhibits relative proportions of  $\leq 60\%$   $\kappa$  light chains and  $\geq 40\%$   $\lambda$  light chains.

5. A transgenic mouse according to claim 1, wherein the mouse includes a HuIg $\lambda$  YAC that accommodates a 380 Kb region of the human  $\lambda$  light chain locus in authentic configuration with all V $\lambda$  genes of cluster A, the J $\lambda$ - C $\lambda$  segments and the 3' enhancer.
6. A transgenic mouse according to claim 5, wherein the HuIg $\lambda$  YAC is shown in Figure 1.
7. A method for producing a transgenic mouse according to claim 1, comprising:
  - (a) introducing a HuIg $\lambda$  YAC into murine embryonic stems cells; and
  - (b) deriving a transgenic mouse from the cells of step (a).
8. The method of claim 7, wherein a HuIg $\lambda$  YAC of about 410Kb that can accommodate a 380 Kb region (V $\lambda$ - JC $\lambda$ ) of the human  $\lambda$  light chain locus with V, J and C genes in germline configuration is introduced into said stem cells.
9. The method according to claim 7 wherein two copies of the neomycin resistance gene (NEO<sup>r</sup>) are site-specifically integrated into the ampicillin gene on the left (centromeric) YAC arm in order to permit selection.

10. The method according to claim 7, wherein YAC-containing yeast cells are fused with HM-1 embryonic stem (ES) cells and G418 resistance colonies are picked and analysed 2-3 weeks after protoplast fusion.
11. The method according to claim 7, wherein ES cells containing a complete HuIg $\lambda$  YAC copy are used for blastocyte injection to produce a chimeric animal.
12. The method according to claim 11, wherein breeding of a chimeric animal with a Balb/c mouse results in germline transmission.
13. The method according to claim 12, comprising breeding the mouse with  $\kappa^{-/-}$  mice to establish lines of transgenic mice.
14. A hybridoma obtainable from a three month old HuIg $\lambda$  YAC/ $\kappa^{+/-}$  mouse by fusion of splenocytes with NSO myeloma cells, and subsequent selection of single clones.
15. Antibodies obtained from a hybridoma according to claim 14.

16. A transgenic mouse comprising as a translocus a yeast artificial chromosome (YAC) of greater than 100Kb which contains a proportion of the human V $\lambda$  genes proximal to the J $\lambda$ -C $\lambda$  cluster in germline configuration.
17. The transgenic mouse according to claim 16, wherein the YAC includes a 380 Kb region of the human Ig $\lambda$  locus in authentic configuration with most V $\lambda$  genes of cluster A, J $\lambda$ -C $\lambda$  segments and the 3' enhancer.
18. A transgenic mouse comprising variable, joining and constant genes of the human  $\lambda$  light chain locus as a transgenic locus on a YAC, wherein B cells of said mice rearrange said  $\lambda$  light chain genes and the mice express serum immunoglobulins containing human  $\lambda$  light chains.
19. The transgenic mouse comprising human  $\lambda$  light chain genes according to claim 16, wherein the  $\lambda$  translocus is rearranged with similar efficiency as endogenous mouse  $\kappa$  and at the same time as or before the endogenous  $\kappa$  locus.
20. The transgenic mouse comprising human  $\lambda$  light chain genes according to claim 16, wherein the endogenous  $\kappa$  locus has been silenced, and the mouse expresses serum immunoglobulins containing human  $\lambda$  light chains.

21. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 16, further comprising human heavy chain genes as a second transgenic locus integrated on a separate YAC, wherein the mouse expresses serum immunoglobulin molecules containing combinations of human heavy and  $\lambda$  light chains.
22. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 21, wherein the second transgenic locus carries a diversity of human heavy chain constant region genes, including  $\mu$ ,  $\delta$  and  $\gamma$  genes.
23. The transgenic mouse carrying human  $\lambda$  light chain genes and human heavy chain genes according to claim 22, wherein the heavy chain transgenic locus carries a diversity of human heavy chain constant region genes, including  $\mu$ ,  $\delta$  and  $\gamma$  genes, in authentic germline configuration.
24. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 16, further comprising human  $\kappa$  light chain genes as a second transgenic light chain locus integrated on a separate YAC, wherein the mouse expresses serum immunoglobulin molecules containing human  $\kappa$  and  $\lambda$  light chains.
25. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 16, further comprising human heavy chain genes as a second transgenic locus and human  $\kappa$  light chain genes as a third transgenic locus, wherein the mouse

expresses serum immunoglobulin molecules containing human heavy chains in combination with human  $\kappa$  or  $\lambda$  light chains.

26. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 16, wherein expression of the endogenous mouse heavy and/or light chain loci has been prevented through gene targeting or other means and which expresses serum immunoglobulin containing human heavy and/or light chains and which are deficient in production of mouse immunoglobulin.
27. A transgenic mouse carrying human  $\lambda$  light chain genes in which expression of the human  $\lambda$  locus is equal to or greater than that of the endogenous or transgenic human  $\kappa$  locus.
28. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 27, wherein the  $\lambda$  translocus has been bred to homozygosity.
29. The transgenic mouse carrying human  $\lambda$  light chain genes according to claim 27, wherein the rearranged variable genes in the  $\lambda$  translocus are subject to somatic hypermutation.
30. A method for production of human antibodies comprising stimulating with antigen transgenic mice incorporating human  $\lambda$  light chain genes into their genome and collecting the human antibodies which bind to the antigen.

31. A method for production of human monoclonal antibodies from transgenic mice and immunised as in claim 30, by creation of hybridomas through fusion to an appropriate mouse myeloma cell line.
32. Human monoclonal antibodies comprising human heavy and light chains of diverse isotypes and chain combinations produced from transgenic mice carrying the human  $\lambda$  translocus.
33. Human monoclonal antibodies according to claim 32, wherein the variable regions of the human  $\lambda$  light chains have undergone somatic mutation.
34. Human monoclonal antibodies according to claim 32, wherein the antibodies have an affinity for antigen of greater than  $10^{-8}$  M.